Diastereo- and Enantioselective Copper-Catalyzed Intramolecular Carboamination of Alkenes for the Synthesis of Hexahydro-1H-benz[f]indoles

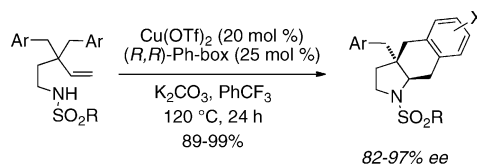Lei Miao, Imranul Haque, Maria R. Manzoni,[†] Weng Siong Tham, and Sherry R. Chemler*

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ABSTRACT

A new method for the enantioselective synthesis of hexahydro-1H-benz[f]indoles is described. This copper-catalyzed enantioselective intramolecular alkene carboamination process can install vicinal tertiary and quaternary carbon stereocenters with high levels of diastereo- and enantioselectivity. The C−C bond-forming component of the reaction constitutes a C−H functionalization and no electronic activation of the aryl ring that undergoes addition is required. A known 5-HT$_{1A}$ receptor antagonist was synthesized efficiently using this method.

The intramolecular carboamination of alkenes is an attractive method for the synthesis of nitrogen heterocycles.[1] This reaction has benefited particularly from methods involving palladium, copper and gold catalysis.[2,3] In recent years, the catalytic asymmetric carboamination has been actively pursued. One approach involves the doubly intramolecular enantioselective carboamination wherein intramolecular alkene amination is followed by addition of the resulting reactive carbon intermediate to a π-bond tethered through the N-substituent. In this manner, Pd(II)[2c] and Cu(II)[3a] complexes have catalyzed formation of chiral bicyclic lactams and sultams, respectively.

We desired to apply the copper-catalyzed carboamination reaction to the synthesis of other nitrogen heterocycles and believed that the proposed carbon radical intermediate,[3c] for example, **A** (Scheme 1), could add to other nearby π-bonds.

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(2) Recent palladium-catalyzed carboaminations/carbonylations: (a) Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, *74*, 9274. (b) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157. (c) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 5626. (d) Scarborough, C. C.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 3251. (e) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (f) Scarborough, C. C.; Bergant, A.; Sazama, G. T.; Guzei, I. A.; Spencer, L. C.; Stahl, S. S. *Tetrahedron* **2009**, *65*, 5084. (g) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488. A gold-catalyzed carboamination: (h) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474.

(3) Copper-catalyzed carboaminations: (a) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (b) Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.* **2009**, *351*, 467. Cu(II)-promoted carboaminations: (c) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896. (d) Fuller, P. H.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 5477.
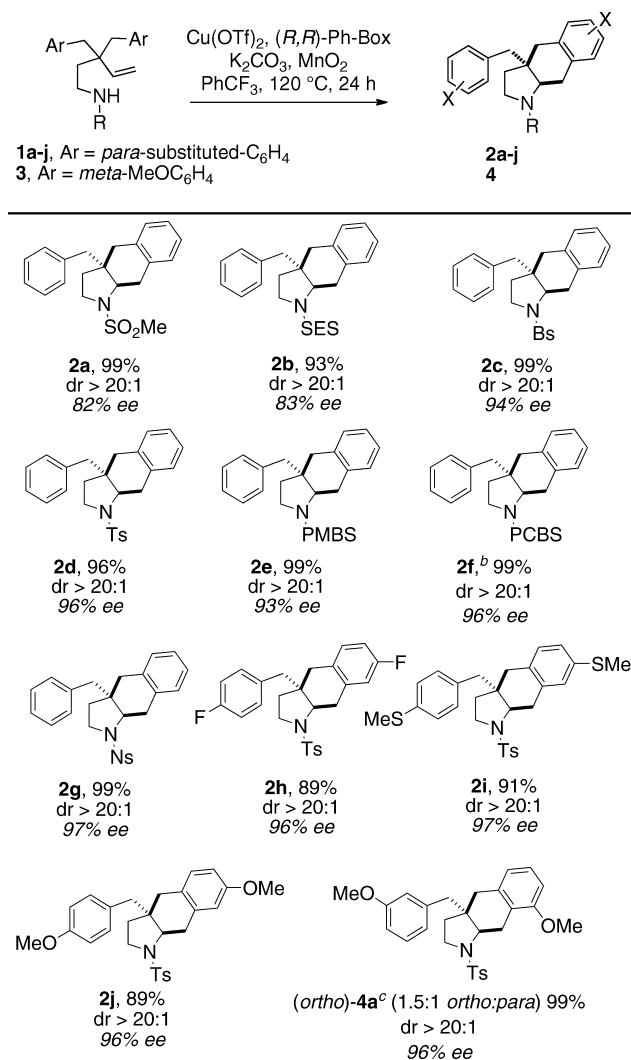
Scheme 1. Benz[f]indole via Carboamination Sequence
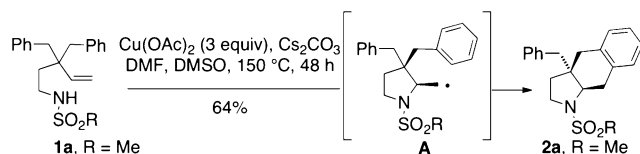
This reaction could in principle be (1) chemoselective, choosing radical addition either to an *N*-arylsulfonyl ring (as previously reported)[3a] or an aromatic ring at the allylic position (as in Scheme 1), (2) diastereoselective, choosing between formation of either a cis or trans ring fusion, and (3) enantioselective, catalyzed by a chiral copper(II)•ligand complex. The desired carboamination product **2** constitutes an otherwise difficult to access hexahydro-1*H*-benz[f]indole ring system and contains vicinal quaternary and tertiary carbon stereocenters. Some benz[f]indoles have demonstrated biological activity as dopamine antagonists[4] and as anticancer agents.[5] Surprisingly few methods for the synthesis of hexahydro-1*H*-benz[f]indoles have been reported.

Our initial forays into the copper-promoted carboamination of *N*-mesyl substrate **1a** were promising. Using 300 mol % of Cu(OAc)$_2$, the cis-fused hexahydrobenz[f]indole **2a** was obtained in 64% yield with >20:1 diastereoselectivity (Scheme 1).[6] Encouraged by this result, we submitted **1a** to catalytic, enantioselective conditions.[3a] To our delight, we obtained a 99% yield and 82% ee, with >20:1 diastereoselectivity using 20 mol % Cu(OTf)$_2$, 25 mol % (*R, R*)-Ph-box, 300 mol % MnO$_2$ at 120 °C in PhCF$_3$ for 24 h (Figure 1, **2a**).

The trimethylsilylethylsulfonyl substrate **1b** (R = SES) underwent the reaction with equal efficiency (Figure 1, **2b**). Various arylsulfonyl substrates **1c−1g** (R = Bs, Ts, PMBS, PCBS, Ns) provided hexahydro-1*H*-benz[f]indole adducts **2c−2g** with even higher enantioselectivity (94−97% ee) and no trace of the sultam[3a] regioisomer. Substrates **1h−1j** with para aryl ring substitution (X = F, SMe, OMe) provided uniformly high yields and enantioselectivities. The *meta*-MeO substrate **3a** gave the benz[f]indoles **4** as a 1.5:1 mixture of ortho and para regioisomers (with respect to aryl addition).[3c]

Interestingly, substrates with ortho substitution, **5a** and **5b**, gave regioisomers **6** and **7** where **7** is the result of a rearrangement where an aryl substituent has apparently shifted to the meta-position. This can be explained by a mechanism involving *ipso*-addition[3d,7] followed by 1,2-alkyl shift (Scheme 2). A similar rearrangement occurred with the *p*-CF$_3$-substituted substrate **1k**, which gave a 3:1 mixture of products **2k** and **8**, the rearrangement product.

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(5) Park, H. J.; Lee, H.-J.; Min, H.-Y.; Chung, H.-J.; Suh, M. E.; Park-Choo, H.-Y.; Kim, C.; Kim, H. J.; Seo, E.-K.; Lee, S. K. *Eur. J. Pharmacol.* **2005**, 527−31, and references therein.

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(7) Gonzales-Lopez de Turiso, F.; Curran, D. P. *Org. Lett.* **2005**, *7*, 151.

Figure 1. Enantioselective carboamination scope. [a] 20 mol % Cu(OTf)$_2$ and 25 mol % (*R,R*)-Ph-Box were combined in PhCF$_3$ (0.1 M w/r to **1**) and heated at 60 °C for 2 h in a pressure tube, then **1**, K$_2$CO$_3$ (100 mol %), MnO$_2$ (300 mol %) were added and the reaction was heated at 120 °C for 24 h. Yield refers to product isolated from flash chromatography on SiO$_2$. Enantioselectivity (%ee) was determined by chiral HPLC. [b] Reaction run at 110 °C. [c] Yield is for combined regioisomeric mixture, dr and %ee were the same for both isomers. SES = trimethylsilylethlysulfonyl, Bs = benzenesulfonyl, PMBS = 4-methoxybenzenesulfonyl, PCBS = 4-chlorobenzenesulfonyl, Ns = 4-nitrobenzenesulfonyl.

Upon the basis of these examples, it appears the propensity to undergo *ipso* rather than direct ortho substitution may be influenced by steric (in the case of ortho substituted) and electronic (in the case of the 4-CF$_3$ substituent) factors. No regioisomers were observed in products **2a−j** and direct substitution without going through an *ipso* intermediate is inferred for these compounds. Ortho substitution causes a decrease in available ortho addition sites while the highly electron-withdrawing 4-CF$_3$ group may influence the relative size of the orbital coefficients at the carbons that undergo addition of the electron-rich primary radical.

Scheme 2. Addition and Rearrangement
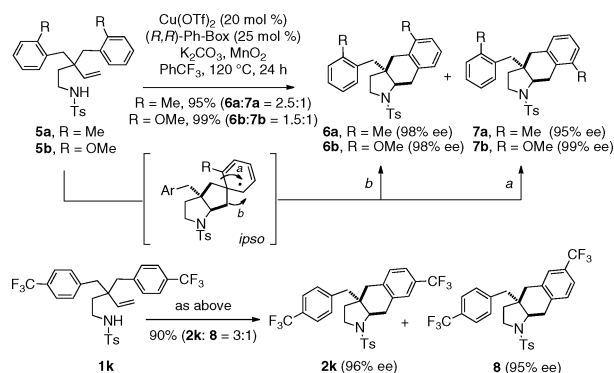
Transition state **B** and intermediate **A** can be used to rationalize the enantio- and diastereoselectivity of the reaction (Scheme 3). This model of enantioinduction is consistent with

Scheme 3. Transition State Model for Enantioselectivity
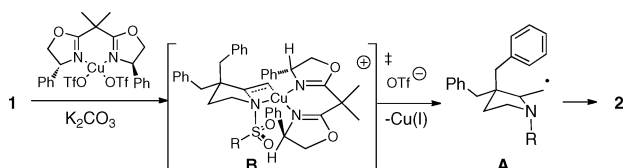
our other copper-catalyzed reactions where the *N*-substituent minimizes interaction with the closest bis(oxazoline) substituent.[3a,8] The diastereoselectivity arises from the carbon radical of **A** adding to the aryl ring it is cis to. The structures of **2a**, **6a**, **7a** and **8** were assigned by X-ray crystallography. The absolute and relative stereochemistry of the other adducts in Table 2 were assigned by NOE and by analogy (see Supporting Information).

We also explored the catalytic, diastereoselective carboamination reactions of the monobenzylated alkenyl sulfonamides **9** (Scheme 4). It was necessary to use the *N*-mesyl derivatives of these substrates as the *N*-tosyl group competes successfully for addition of the carbon radical intermediate in these cases. The *N*-mesyl substrates **9a** and **9b** provided the *trans*-fused carboamination products **10** as the major diastereomers. Transition state **C**, which places the benzyl

(8) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638.

Scheme 4. Diastereoselective Carboaminations
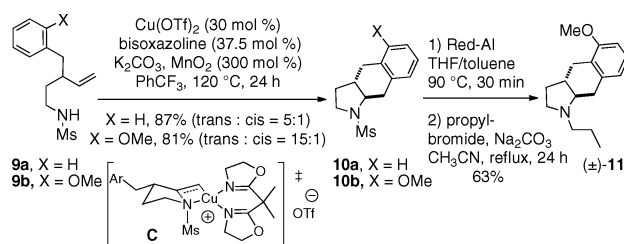
substituent in a pseudoequatorial position, rationalizes the formation of the major diastereomers. The ortho-substituted **9b** does not form products resulting from *ipso* substitution and rearrangement. This is likely because the formation of a trans-fused five-membered ring intermediate involved in this *ipso* substitution is more difficult to form than the trans-fused six-membered ring that would result from direct ortho addition that leads to the observed product. In the case of **5**, a more favorable cis-fused spirocyclic intermediate (Scheme 2) can be formed.

Conversion of *ortho*-methoxy adduct **10b** to the known 5-HT$_{1A}$ receptor antagonist[4] **11** was accomplished by removal of the mesyl group with Red-Al followed by *N*-alkylation (63%, two steps). Our synthesis of (±)-**11** is 8 steps from γ-butyrolactone (24% overall yield) an improvement over its previous synthesis.[4]

In conclusion, this intramolecular alkene carboamination provides hexahydro-1*H*-benz[*f*]indoles in a concise and enantioselective manner. New vicinal quaternary and tertiary stereocenters can be formed in this reaction. The aromatic rings that undergo addition do not require any specific activating functionality and the C−C bond-forming step constitutes a C−H functionalization.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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